

BIOGRAPHICAL SKETCH

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NAME: **Rajeshwar Rao Tekmal**

eRA COMMONS USER NAME: **rtekmal**

POSITION TITLE: **Professor of Ob-Gyn; Carl J. Pauerstein Professor of Rep. Research**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Osmania University, Hyderabad, India	B.Sc.	1975	Biology
Osmania University, Hyderabad, India	M.Sc.	1977	Biological Sciences
Kurukshetra University (Natl. Dairy Res. Inst.), Kurukshetra, India	Ph.D.	1982	Biochemistry
Michigan State University, East Lansing, MS	Postdoc	1984	Molecular Genetics
Univ. of Mississippi Medical Ctr., Jackson, MS	Postdoc	1987	Molecular Biology

A. Personal Statement

I have training in biochemistry, cancer biology, endocrinology and molecular biology and extensive experience and expertise in developing preclinical models for testing the effect of estrogen, growth factors and oncogenes on the initiation and progression of breast cancer. In addition to mammary/breast cancer models, I use cervical and ovarian cancer models to understand the role of estrogen and its receptors in the etiology of these cancers. As a PI or Co-PI/investigator on several university- and NIH funded grants, I have expanded my research to include preclinical and transgenic models for breast and other malignancies. In early independent research career, I was involved in the discovery of novel mouse mammary tumor virus integration locus (int-h/int-5) that was responsible for the induction of aromatase (estrogen biosynthase). My work using *in vivo* model system we developed is the first one to show local estrogen is responsible for initiation of breast cancer. We are also the first one to show estrogen receptor (ER α) is critical for mammary tumorigenesis irrespective of high local estrogen. My other research interests also include investigating the importance of ER/novel coactivator-mediated mechanisms in the induction of aromatase in breast and other gynecological cancers and cell cycle progression, chromatin remodeling and extra-nuclear signaling. Our ongoing studies are the first one to demonstrate the importance of ER β agonists in overcoming resistance to endocrine therapies in breast cancer models. During this time, I have served as PI/co-PI of several NIH, DOD-BCRP, Komen and other foundation/pharmaceutical funded projects and served in study sections including NIH, DOD-BCRP, Komen and other international agencies. My extensive experience in mammary biology, hormonal carcinogenesis, ER/estrogen actions as well as experience in hormone-mediated therapies make me particularly well suited to lead this and other projects.

B. Positions and Honors

1987-1989 Asst. Research Scientist, Dept. of Biological Sciences, Oakland University,
Rochester, MI

1989-1995 Asst. Professor, Dept. of OB-GYN, Univ. of Texas Health Science Center, San
Antonio, TX

1995-2003 Professor/Assoc. Prof.(Tenured), Dept. of GYN and OB, Emory Univ., Atlanta, GA.

2002-2003 Breast Cancer Program Leader, Winship Cancer Institute, an NCI-designated Clinical Cancer Center, Emory University, Atlanta, GA.

2003-Present: Professor (Tenured) Dept. of Ob-Gyn, Univ. of Texas Health Science Center at San Antonio, TX

2003 – Present: Director, Division of Research, Dept. of OB-GYN, Univ. of TX Health Sci. Ctr. at San Antonio, TX

2005-Present: Carl J. Pauerstein Professorship in Reproductive Research

2003- Present Member, Cancer Therapy and Research Center at UTHSCSA, San Antonio, TX

2004- Present Faculty Member, Integrated Multidisciplinary Graduate Program, Univ. of Texas Health Sci. Center at San Antonio, TX

2006-Present Theme Leader (Women's Cancer), CTRC, an NCI-designated Clinical Cancer Center at UTHSCSA

Awards and Honors: 1972-1975, Osmania University Undergraduate Merit Scholarship; 1977, Graduated M.Sc. First Class with distinction; 1977-1981, Indian Council of Agriculture Research Pre-doctoral Merit Scholarship; 1992-1997, FIRST NIH/NCI Award Grant; 1993, San Antonio Area Foundation Research Grant Award, 1998, AACR Young Investigator Award (Fellow: Kiran Gill); 2000, AACR Young Investigator Award (Fellow: Nameer Kirma); 2004, ASRM Best Poster Presentation Study Award (Fellow: Ya-Guang Liu); 2006, AACR-Aflac Young Investigator Award (Fellow: Jatin Nagpal); 2009, V-Foundation/Kay-Yow Cancer Fund (NCAA) grant award; 2012 & 13, AACR-Minority Serving Institute Faculty Scholar Award.

Study Sections: 1994-97: Member, Mol. Biol. DOD-BCRP; 1998-2002: Member, NIH Reproductive Endocrinology; 2000: Member, NIH Special study section on "Insight awards to stamp out breast cancer"; 2000-2003: Member, NIH Special Emphasis Panel (Endocrinology, Oncology Sciences); 2001: Member, ACS Molecular genetics and oncogenes; 2004: Member, California State Breast Cancer Research Program Review Panel; 2004-2008: Member, Susan Komen Breast Cancer Foundation Grants Program; 2004: Member, NIH, ZRG1 CDP Oncological Sciences IRGC; 2005: Member, NIH, ZRG1 EMNR-D 02 S; 2005: Member, NIH, ZRG1 F09 (20) L Oncological Sciences IRG; 2006: Member, NIH (ZRZ1 ONC-T (03); 2006: Member, NIH (ZRZ1 F06-G 20 L); 2008-2010: Member, Molecular biology/cancer genetics,) DOD-BCRP; 2008: Member, Breast Cancer Foundation and AACR grant program; 2008-present: External Reviewer, AIRC - Italian Association for Cancer Research; 2009 & 2014: External Reviewer, Research Grants Council, Hong Kong, PRC; 2009: Member, NIH (ZRZ1 OTC-K (58) Oncology -2: Translational Clinical IRG; 2010 & 12: External Reviewer, Health Research Board, Ireland, UK; 2010: External Reviewer, Wellcome Trust/Department Biotechnology, Govt. of India; 2010: Florida State Cancer Research Grants; 2011: Member, NIH (ZRG1) EMNR-C, Endocrinology, Metabolism and Reproduction; 2011: Member, NIH, ICER; 2013: Member, NIH, ZCA1 GRB-I (M1) R Provocative Questions: Cancer Therapy and Outcomes; 2013: Member, NIH, ZRG1 OTC-T (12) Small Business: Cancer Drug Development & Therapeutics; 2014: Member, NIH, ZCA1 SRLB-5 (M2) S: Cancer Etiology; 2014-present: Member, NIH, ZRG1 Small Business: Cancer Drug Development & Therapeutics

Editorial: 1997-Present: Managing Editor (Hormonal Carcinogenesis), Frontiers in Bioscience; **2007-2009: Cancer Research Associate Editor; 2007-14 & 2016-17: Editorial Board, Cancer Research of AACR.** I also serve on the editorial boards of several online journals. In addition, I am regular reviewer for several leading biomedical journals.

Memberships: Member, American Association of Cancer Research; Member, Endocrine Society, Society for Gynecological Investigation

C. Contributions to Science: My postdoctoral work focused on establishing a cloning system work ligninolytic filamentous fungus at Michigan State University. My research efforts at Univ. of

MS medical center focused on investigating the role of eukaryotic protein synthesis elongation factor regulation during different phases of cell growth.

1. My early independent career publications focused on the discovery of novel mouse mammary tumor virus (MMTV) integration locus (*int-5*) that was responsible for the induction of aromatase (estrogen biosynthase) gene. Unlike other oncogenic viruses, MMTV-mediated etiology of mammary cancer involves the activation cellular genes at the integration locus by MMTV-LTR promoter/enhancer elements. One such example is *wnt* genes. *Int-5* locus we discovered MMTV is integrated in the 3' end of aromatase gene in BALB/c mice that is responsible estrogen-driven mammary cancer in these mice.

- a. Morris VL, **Rao TR**, Kozak CA, Gray DA, Lee Chan EC, Cornell TJ, Taylor CB, Jones RF, McGrath CM.: Characterization of *Int-5*, a locus associated with early events in mammary carcinogenesis. *Oncogene Res.* 1991; 6(1):53-63. PMID: 1705320. **Citations prior to 1993 are listed as Rao, TR**
- b. Durgam VR, **Tekmal RR**.: The nature and expression of *int-5*, a novel MMTV integration locus gene in carcinogen-induced mammary tumors. *Cancer Lett.* 1994, 87(2):179-86. PMID: 7812938
- c. **Tekmal RR**, Durgam VR.: The overexpression of *int-5*/Aromatase, a novel MMTV integration locus gene, is responsible for D2 mammary tumor cell proliferation. *Cancer Lett.* 1995, 88(2):147-55. PMID: 7874687
- d. Drugam VR, Easton JA, Surya R, **Tekmal RR**.: Structure of the *int-5*, a novel MMTV integration genomic locus containing mouse early transposon LTR homology region. *Biochim Biophys Acta.* 1995, 1263(1):89-92. PMID: 7632740

2. Estrogen not only contributes to the progression of breast cancer, but it is also synthesized by the breast tumors. Though pharmacological doses of estrogen is known to act as carcinogen in rodents, but there is no direct evidence of estrogen synthesized in the mammary/breast tissues is responsible for breast cancer initiation in men and women. We are the first to one provide a direct *in vivo* biological evidence that estrogen made with in the breast tissue is responsible initiation of mammary cancer in males and females using transgenic animal models we have developed. Change in the hormone milieu also results in induction of gynecomastia and Leydig cell testicular cancer in male mice. Estrogen receptor- α is critical for *in situ* estrogen-driven mammary carcinogenesis.

- a. Tekmal RR, Ramachandra N, Gubba S, Durgam VR, Mantione J, et al.: Overexpression of *int-5*/aromatase in mammary glands of transgenic mice results in the induction of hyperplasia and nuclear abnormalities. *Cancer research.* 1996; 56(14):3180-5. PMID: 8764102
- b. Tekmal RR, Kirma N, Gill K, Fowler K.: Aromatase overexpression and breast hyperplasia, an *in vivo* model--continued overexpression of aromatase is sufficient to maintain hyperplasia without circulating estrogens, and aromatase inhibitors abrogate these preneoplastic changes in mammary glands. *Endocrine-related cancer.* 1999; 6(2):307-14. PMID:10731124
- c. Fowler KA, Gill K, Kirma N, Dillehay DL, Tekmal RR.: Overexpression of aromatase leads to development of testicular Leydig cell tumors: an *in vivo* model for hormone-mediated Testicular Cancer. *The American journal of pathology.* 2000; 156(1):347-53. PMID: 10623684
- d. Tekmal RR, Liu YG, Nair HB, Jones J, Perla RP, et al.: Estrogen receptor alpha is required for mammary development and the induction of mammary hyperplasia and epigenetic alterations in the aromatase transgenic mice. *The Journal of steroid biochemistry and molecular biology.* 2005; 95(1-5):9-15. PMID: 15955696

3. In collaboration with several investigators, I was involved in establishing the oncogenic role of novel estrogen receptor coactivator using our *in vivo* model systems. Expression of Proline

glutamic acid and leucine rich protein (PELP-1) is commonly deregulated in breast and other cancers. PELP-1 overexpression is responsible for mammary tumor formation and is also responsible for regulation of local estrogen synthesis in breast tumors. PELP-1 has potential therapeutic target is being evaluated using small molecular inhibitor.

- a. Rajhans R, Nair S, Holden AH, Kumar R, Tekmal RR, Vadlamudi RK. Oncogenic potential of the nuclear receptor coregulator proline-, glutamic acid-, leucine-rich protein 1/modulator of the nongenomic actions of the estrogen receptor. *Cancer Res.* 2007, 67(11):5505-12. PMID: 17545633
- b. Vadlamudi RK, Rajhans R, Chakravarty D, Nair BC, Nair SS, Evans DB, Chen S, Tekmal RR.: Regulation of aromatase induction by nuclear receptor coregulator PELP1. *J Steroid Biochem Mol Biol.* 2010, 118(4-5):211-8. PMID: 19800002
- c. Roy SS, Gonugunta VK, Bandyopadhyay A, Rao MK, Goodall GJ, Sun LZ, Tekmal RR, Vadlamudi RK.: Significance of PELP1/HDAC2/miR-200 regulatory network in EMT and metastasis of breast cancer. *Oncogene.* 2014, 33(28):3707-16. PMID: 23975430
- d. Cortez V, Samayoa C, Zamora A, Martinez L, Tekmal RR, Vadlamudi RK.: PELP1 overexpression in the mouse mammary gland results in the development of hyperplasia and carcinoma. *Cancer Res.* 2014, 74(24):7395-405. PMID: 25377474

4. Estrogen mediated actions are mediated by its two its two receptors ER α and β . While ER α is known for its involvement in initiation of progression of breast cancer, whereas ER β has no significant effect on mammary development but it appear to act as antiproliferative/tumor suppressor in blocking the progression of breast cancer. Cross talk between ER α and growth factor-signaling, constitutively activating ER α mutations and alteration in the ratio of ER α /ER β are implicated as the major causes for development of resistance. Using both *in vivo* and *in vitro* models system our studies have shown that ER β acts has tumor suppressor and induction/activation of ER β by its agonists also results in blocking/delaying the development of resistance to aromatase inhibitors (AI). Combination therapy with AI and ER β agonist appear to resensitize breast tumor that are resistant to AI. In addition, our collaborative studies have shown that ER β and its agonist mediated acts also responsible regulation of ER β phosphorylation.

- a. **Tekmal** RR, Nair HB, Perla RP, Kirma N.: HER-2/neu x aromatase double transgenic mice model: the effects of aromatase overexpression on mammary tumorigenesis. *J Steroid Biochem Mol Biol.* 2007,106 (1-5):111-8. PMID: 17604617
- b. Nair HB, Kirma NB, Ganapathy M, **Vadlamudi** RK, **Tekmal** RR.: [Estrogen receptor- \$\beta\$ activation in combination with letrozole blocks the growth of breast cancer tumors resistant to letrozole therapy.](#) *Steroids.* 2011, 76(8):792-6. PMID: 21477609
- c. Nair HB, Perla RP, Kirma NB, Krishnegowda NK, Ganapathy M, Rajhans R, Nair SS, Saikumar P,**Vadlamudi** RK, **Tekmal** RR.: [Estrogen receptor-beta mediates the protective effects of aromatase induction in the MMTV-Her-2/neu x aromatase double transgenic mice.](#) *Horm Cancer.* 2012, 3(1-2):26-36. PMID: 22006184
- d. Yuan B, Cheng L, Chiang HC, Xu X, Han Y, Su H, Wang L, Zhang B, Lin J, Li X, Xie X, Wang T, **Tekmal** RR, Curiel TJ, Yuan ZM, Elledge R, Hu Y, Ye Q, Li R.: [A phosphotyrosine switch determines the antitumor activity of ER \$\beta\$.](#) *J Clin Invest.* 2014,124(8):3378-90. PMID: 24960160

5. Obesity is associated with a worse breast cancer prognosis, particularly in ER α positive, postmenopausal patients. We hypothesized that this is mediated in part by an elevation in breast cancer cell cyclooxygenase-2 (COX-2) expression and prostaglandin E2 (PGE2) production that results in greater local pre-adipocyte aromatase expression. These collaborative studies have shown that that obesity-associated systemic IL-6 indirectly enhances pre-adipocyte aromatase expression via increased breast cancer cell PGE2 production. In addition, our findings in experiments with RAD-001 indicate that combination treatment with mTOR inhibitors and with AI or antiestrogens reverses the Akt-mediated resistance and

restores responsiveness to antiestrogens. Concurrent ER and mTOR inhibition is therefore an effective strategy to overcome growth factor-induced resistance and bears significant implications for optimal clinical development of these agents in breast cancer treatment. These findings also raise the use of COX-2 inhibitor/aromatase inhibitor combination therapy in the obese postmenopausal patient population.

- a. Beeram M, Tan QT, **Tekmal RR**, Russell D, Middleton A, DeGraffenried LA.: Akt-induced endocrine therapy resistance is reversed by inhibition of mTOR signaling. *Ann Oncol.* 2007 18(8):1323-8. PMID: 17693645
- b. Bowers LW, Maximo IX, Brenner AJ, Beeram M, Hursting SD, Price RS, **Tekmal RR**, Jolly CA, deGraffenried LA.: NSAID use reduces breast cancer recurrence in overweight and obese women: role of prostaglandin-aromatase interactions. *Cancer Res.* 2014, 74(16):4446-57. PMID: 25125682
- c. Gonugunta VK, Sareddy GR, Krishnan SR, Cortez V, Roy SS, **Tekmal RR**, Vadlamudi RK.: Inhibition of mTOR signaling reduces PELP1-mediated tumor growth and therapy resistance. *Mol Cancer Ther.* 2014, 13(6):1578-88. PMID: 24688046
- d. Bowers LW, Brenner AJ, Hursting SD, **Tekmal RR**, deGraffenried LA.: Obesity-associated systemic interleukin-6 promotes pre-adipocyte aromatase expression via increased breast cancer cell prostaglandin E2 production. *Breast Cancer Res Treat.* 2015, 149(1):49-57. PMID: 25476497

Completed List of Published Work in My Biobibliography: *Citations, prior to 1993 are cited as Rao, TR.*

<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47757378/?sort=date&direction=ascending>

D. Research Support:

Ongoing Research Projects:

DOD BCRP-151884 W81XWH-16-1-0294	Prevention of breast cancer and therapy resistance using novel therapeutic approaches Principal Investigator: Dr. Rajeshwar Rao Tekmal 07/01/2016-06/30/2019
SOM Women's Health Pilot grant	Role of CD44 and RHAAM in endometrial pathogenesis Principal Investigator: Dr. Rajeshwar Rao Tekmal 10/01/2016- 09/30/2018
NIH R21	Re-sensitizing ER-alpha mutant breast cancer cells to hormonal therapy Investigator: Dr. Rajeshwar Rao Tekmal (PI: Rong Li) 07/01/2016- 01/30/2018
Bill & Melinda Gates Foundation Evestra, Inc	Testing of novel steroid compounds for their efficacy as a long-acting agents for birth control Principal Investigator: Dr. Rajeshwar Rao Tekmal 12/01/2015-02/28/2018
NIH/NCI R01CA178499	Novel ER beta agonists for the treatment of gliomas Investigator: Dr. Rajeshwar Rao Tekmal (Pl. Vadlamudi) 09/04/2014-08/31/2019

The major goal of this project is (1) To test the significance and therapeutic efficacy of ER β agonists to inhibit the growth of GBM (2) To determine the molecular mechanism(s) of ER β agonists in the suppression of GBM (3) To investigate the role of ER β agonists in differentiation of Glioma Stem Cells (GSCs).

CPRIT
DP150096

Bridging the Gap Award

Investigator: Dr. Rajeshwar Rao Tekmal (P.I.: Dr. Ratna K. Vadlamudi)
03/01/2015- 02/28/2018

This project examines the therapeutic role of estrogen receptor coregulator to target hormone therapy resistant breast cancer. Work focuses on optimizing lead compounds and establishes the biological activity and preclinical models.

NIH 5 KL2 TR00118

Role of hyaluronic acid pathway and its involvement in the early endometriotic lesion formation: IIMS Mentored Research and Career Development (KL2) Program in Clinical and Translational Science Award grant to Faculty Scholar

KL2-Scholar: Jennifer Knudtson, M.D., Mentor: Dr. Rajeshwar Rao Tekmal

5/1/2016-4/30/2018

ASRM Research
New Investigator

Early Endometriotic Lesion Formation

Knudtson (PI); **Mentor: Dr. Rajeshwar Rao Tekmal**

7/1/2015-7/1/2018

The goal of this study is to confirm the findings from the CD44 Knockout mice study looking at overexpression of the different CD44 splice variants that are increased in endometriotic lesion formation.

Endometriosis
Foundation of America

Estrogen Receptors in the Early Endometriotic Lesion

Knudtson(PI); **Mentor: Dr. Rajeshwar Rao Tekmal**

3/1/2017-2/28/2018

This study will investigate the role of estrogen receptor beta and alpha in human menstrual endometrium and the ectopic endometriotic lesion

Research Interests of Rajeshwar Rao Tekmal, Ph.D.

For the last ~30 years my research has focused on breast and other gynecological malignancies as well as on benign women's disease such as endometriosis.

Breast Cancer: For the past several years (25 plus) the special emphasis of my research is to understand the importance of local estrogen (as a result of aromatase overexpression or induction) in breast cancers. My work using our novel *in vivo* model is the first one to show local estrogen is responsible for initiation of breast cancer. We are also the first one to show estrogen receptor (ER α) is critical for mammary tumorigenesis irrespective of high local estrogen. Our *in vivo* studies with double transgenic models have provided first genetic evidence that high ER β (change in ER α / β ratio) protein levels plays an important role in mammary tumorigenesis. . Our ongoing studies are the first one to demonstrate the importance of ER β agonists in overcoming resistance to endocrine therapies in breast cancer models. We are testing the potential use of ER β agonists in the prevention and progression of breast cancer using *in vivo* genetic models.

Cervical Cancer: My laboratory is the first one to show local estrogen plays the important role in the progression of cervical tumors. Ongoing studies are aimed at further investigating the importance of tissue estrogen in cervical malignancy using both *in vitro* and *in vivo* model systems.

Endometrial Cancers: Our laboratory in collaboration with Gynecologic Oncologists is examining the etiological factors that are responsible for the development of endometrial cancer in young women. The special emphasis is on the role of hormones, growth factors and inflammatory cytokines in the initiation and progression of endometrial cancers.

Endometriosis: Dr. Tekmal's group in collaboration with Reproductive Endocrinologists examines the role hyaluronic acid (HA) and its receptors such as CD44 and RHAMM in the formation of early endometriotic lesions using both *in vitro* and *in vivo* genetic models. This project also focuses on the possible therapeutic intervention using small molecules that affects the regulation of HA and its receptor system

These projects provides hands experience to trainees on various molecular, cell biology, tumor biology as well as therapeutic approaches to treat gynecological malignancies and benign women's diseases. Dr. Tekmal is involved in training both basic and clinical fellows and students as well as mentoring junior faculty. Dr. Tekmal's research is funded by both federal, biotech and other sources.